THE EFFECTS OF THE INTRACISTERNAL INJECTION OF KAOLIN AND THE POSSIBILITY OF PRODUCING ARTERIAL HYPERTENSION BY THIS PROCEDURE IN RATS, RABBITS, AND DOGS

BY

EDWARD HOWARD LAMBERT

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Kaolin hypertension, as originally produced and described by Dixon and Heller in 1932, is a sustained elevation of arterial pressure which results in dogs following the intracisternal injection of a suspension of kaolin. In the past several years numerous investigators (5, 8, 11, 18, 21, 22, 23, 28, 29, 32)[1] have confirmed the work of Dixon and Heller with the regular production of this type of hypertension. A temporary elevation of arterial pressure by intracisternal kaolin injection was produced in rats (14, 15) but not in cats (25) by Griffith and his collaborators.

The procedures described for the production of kaolin hypertension are simple (8, 19, 29). No particular precautions have been emphasized. The elevation of blood pressure, usually marked (80 to 100 mm. Hg, systolic pressure), has been reported to develop, apparently in a high percentage of animals injected, after a variable period of time (several hours, Heller [20], to several weeks, Giordano and Galigani [10]). The hypertensive blood pressure level is unstable and associated with increased excitability of the dog (29).

According to the original hypothesis of Dixon and Heller, the hypertension is due to increased intracranial pressure which results when the minute kaolin particles mechanically block the absorption of cerebrospinal fluid from the subarachnoid space. The occurrence of a moderate increase of intraventricular pressure (8, 15, 30, 32) and internal hydrocephalus (8, 18, 15, 11, 32) are the only significant, pathologic changes which have been found to occur regularly.

The original plan of the present investigation was to study the role of the kidney in the pathogenesis of neurogenic hypertension produced by the intracisternal injection of kaolin. Despite the widespread interest in the possible renal origin of essential hypertension in man, recent studies have re-emphasized the prominence of symptoms of central nervous origin in this disease. To correlate these factors it has been suggested that the humoral pressor system of the kidney may be activated through the central nervous system. We proposed to study the possible existence of such a mechanism in experimental neurogenic hypertension.

Kaolin hypertension was selected for this study because intracisternal kaolin injection, especially in the dog, was considered uniformly a simple and reliable method for producing a sustained elevation of arterial blood pressure of central origin. This was not true of the other methods avail-

[1] Numerals in parentheses refer to items in Bibliography, pp. 14-15.

able. Another indication for this selection was that published work indicated, although inconclusively, a participation of the kidney in the pathogenesis of kaolin hypertension (1-5, 11); Tanabe's work (30), however, did not substantiate these findings.

Contrary to our expectation, in preliminary work repeated failures were encountered in attempting to produce hypertension by intracisternal kaolin injection in rats, rabbits, and dogs. The only apparent difference between the procedures used in this work and in published work was in the methods used to measure blood pressure. Especially was this true for the work on the dog. In all successful reports published on kaolin hypertension in the dog the measurement of blood pressure had been made by indirect methods. Our own method was by direct arterial puncture. In view of the fact that the experimental findings reported in studies of kaolin hypertension frequently had been quoted and accepted as support for various hypotheses, the investigation was continued to determine the possibility of producing a significant, persistent arterial hypertension by intracisternal kaolin injection using the newer, more reliable methods of measuring blood pressure.

METHODS

Merck's N. F. kaolin[2] and Collosol kaolin were used in these experiments. Suspensions were prepared in the following ways: (1) crude suspensions were made by shaking kaolin in distilled water or physiological saline solution; (2) suspensions in distilled water, physiological saline solution or 5% acacia solution were made by mixing in a ball mill; and (3) fine suspensions were made by centrifuging crude suspensions or permitting them to stand from 3 to 7 days to allow larger particles to settle out. The suspensions were sterilized by boiling or by autoclaving.

Animals were anaesthetized with ether, pentobarbital, or pentothal for injection of the kaolin suspensions into the cerebello-medullary cistern by suboccipital puncture. The injections were made under sterile conditions after withdrawal of an equal quantity of spinal fluid.

Thirty-one rabbits (2 to 3.5 kg., body weight) received intracisternal injections of 20 to 60 mgm. of Merck's kaolin per kg. of body weight in 0.3 to 0.8 cc. of suspension. Blood pressure was measured without anaesthesia by the abdominal cuff method of McGregor. One to eight measurements were made before kaolin injection and at approximately weekly intervals thereafter.

Ninety-seven white rats (150 to 450 grams, body weight) received intracisternal injections of 10 to 30 mg. of Merck's or Collosol kaolin

[2] Inert hydrated aluminum silicate.

per kg. of body weight. The withdrawal of spinal fluid and injection of kaolin in 0.02 to 0.03 cc. of suspension were made with a single suboccipital puncture using a special two-arm pipette. Arterial blood pressure was measured by the tail plethysmograph method (6) using ether anaesthesia or heat (33) to dilate the tail artery. Readings were made on one to three days before the kaolin injection and subsequently at approximately weekly intervals. In a group of twenty rats the blood pressure was measured by carotid artery cannulation under ether anaesthesia using a high-frequency, glass spoon manometer (24) with photographic recording.

Twenty-nine dogs (8 to 16 kg., body weight) received intracisternal injections of 20 to 40 mg. of Collosol kaolin per kg. of body weight in 0.5 to 4.5 cc. of suspension. The arterial blood pressure was measured without anaesthesia by puncture of the femoral artery with a 20-gauge needle, using an anaeroid manometer (7) or a high-frequency, glass spoon manometer (24) with photographic recording. Routine measurements were made two to three times a week in a quiet room by a single observer to whom the dogs were accustomed. The control period before the kaolin injection varied from 1 to 190 days.

Several indirect (cuff) methods of measuring blood pressure were tested with direct methods on dogs before and after the injection of kaolin.

RESULTS

I. Studies on the Effect of Kaolin Injection in Rabbits

Ten rabbits survived the intracisternal injection of kaolin for five days or more. Six were in good condition. These were observed for 25 to 360 days after injection. In no instance did the blood pressure following intracisternal kaolin injection exceed the range of 80 to 140 mm. Hg, systolic pressure. This was the range of 90 per cent of 83 determinations of blood pressure on 37 untreated, healthy rabbits, and the range of readings obtained by other investigators in normal rabbits using the same method of measuring blood pressure (26).

Attacks of albuminuria frequently accompanied by mild elevations in arterial blood pressure were noted occasionally in both control and kaolin-injected rabbits. No elevation of cerebrospinal fluid pressure, measured intracisternally, was noted in six rabbits following kaolin injection.

Autopsy confirmed the successful subarachnoid injection of kaolin in every case. Various degrees of internal hydrocephalus were noted. Four animals showed softening in the cervical region of the spinal cord. In three animals macroscopic cavitation was present in the region of the central canal.

II. Studies on the Effect of Kaolin Injection in Rats

No difference was noted between a group of 41 rats injected with Merck's N. F. kaolin and another group of 56 injected with Collosol kaolin. A total of 78 rats from both groups survived the intracisternal injection and were in good condition. Following the injections of kaolin, no rats gave blood pressure readings out of the range obtained for untreated rats (60 to 140 mm. Hg, range for 112 normal rats). A few rats showed a slight elevation of pressure (less than 30 mm. Hg) usually in the second or third week. The results were similar in 28 rats when the blood pressure was taken using heat instead of ether to dilate the tail artery.

The reliability of the tail plethysmograph was established by comparison with blood pressure readings obtained simultaneously by cannulation of the carotid artery. Furthermore, the tail plethysmograph satisfactorily demonstrated the occurrence of hypertension of renal origin in rats. As a further test in 20 rats injected with Collosol kaolin, according to the method described by Griffith, the blood pressure was determined by cannulation of the carotid artery, using a glass spoon manometer. No significant elevation of pressure was found in this group. There also was no difference in the pulse curves of kaolin-injected rats and normal untreated rats.

Despite the failure of hypertension to occur, increased pressure of the fluid in the subarachnoid space was observed following the injection of kaolin suspensions. Internal hydrocephalus was present in many animals at autopsy.

III. Studies on the Effect of Kaolin Injection in Dogs

All the mean femoral artery blood pressure readings in 29 dogs before kaolin injection ranged from 88 to 155 mm. Hg (average 115 mm. Hg). Six dogs died within a few days of the injection of kaolin. The 23 surviving animals were observed for 18 to 394 days until they died (6 dogs), were sacrificed, or were subjected to other operative procedures. All the mean blood pressure readings of these dogs after kaolin injection were between 90 and 162 mm. Hg. Nine dogs in this group showed a mild temporary elevation of mean pressure of less than 30 mm. Hg. This elevation reached a maximum in 2 to 24 days and subsided in 3 to 7 weeks. Aside from these temporary alterations the blood pressure remained at the control level throughout the period of observation.

In 6 of the dogs the systolic and diastolic blood pressure levels and the pulse contour were determined routinely with a glass spoon manometer. No significant elevation of blood pressure occurred following kaolin in-

jection in these dogs. There was no characteristic change of the pulse contour.

The effect of kaolin injection on the pulse rate was variable. In most instances there was a definite decrease lasting from one to several days immediately after the injection. This was frequently followed by an increase above the control values. The cerebrospinal fluid pressure (lateral ventricle) ranged from 180 to 240 mm. saline in 6 of 10 dogs tested, 22 to 420 days after kaolin injection. In 10 untreated dogs the pressure in the subarachnoid space ranged from 84 to 115 mm. saline.

Signs of meningeal irritation, with a general increased excitability, were usually present for periods up to 1 month after the injection. Mild ataxia and partial paralysis of the extremities were observed. Loss of weight in one group of 6 dogs was progressive (18 to 50% of original body weight). In another group of 16 dogs loss of 2 to 30% (average 10%) of the original body weight was regained in one to three months.

Post-mortem examination was made of every dog used in these experiments. No abnormalities were noted outside the central nervous system. Kaolin was found matted into a firm, dense, adherent layer about the base of the brain and the upper spinal cord. Smaller amounts were noted over the cerebellum, cerebrum, on the floor of the fourth ventricle and even in the third and lateral ventricles. Various degrees up to rather marked internal hydrocephalus occurred.

In the spinal cord, striking changes occurred which have not been described heretofore in kaolin-injected dogs. Cavitation of the cervical spinal cord involving in some instances almost all of the central gray matter was observed in 14 of 18 dogs after periods of survival of 25 days to 25 months. Areas of softening were noted in association with the cavities, and in 4 dogs softening occurred without cavitation. In microscopic sections gliosis was minimal or absent. The changes result from the severe adhesive spinal arachnoiditis caused by the injected kaolin.

IV. Miscellaneous Experiments in Dogs

Animals which had been observed for some time after kaolin injection were in several instances subjected to other procedures in an attempt to produce arterial hypertension or test the ability of the dogs to become hypertensive by recognized procedures.

1. Attempts to make a second injection of kaolin in four dogs were unsuccessful. Apparently kaolin from the previous injection blocked the subarachnoid space.

2. Ligation of the vertebral arteries and the carotid arteries and their

branches in dogs previously injected with kaolin caused a moderate instability of the blood pressure level, but no significant hypertension.

3. Disagreement exists in the literature as to the ability of section of the moderator nerves to produce a sustained elevation of arterial blood pressure in dogs (16). The effect of excision of the carotid sinuses and section of the aortic depressor nerves was observed in three kaolin-injected dogs in this investigation. Two dogs which had not previously been injected with kaolin showed a similar reaction to this operation. For a period of two to three weeks after the removal of the buffer nerves there was a marked, unstable elevation of blood pressure (up to 210 mm. Hg, mean pressure). Thereafter the blood pressure reached a range (120 to 150 mm. Hg) equal to or only slightly above the preoperative level. Throughout the period of observation the blood pressure of these dogs remained remarkably unstable, increasing as much as 150 mm. Hg in a few seconds as a result of minor disturbances which caused apprehension or attention of the dog without actual struggling. The animals did not have a sustained hypertension. They did have a marked vasomotor instability which was present as long as the dogs were observed (up to 18½ months).

The routine method of measuring blood pressure by a single arterial puncture lasting three to five minutes as used in normal or renal hypertensive dogs was frequently inadequate in these animals. Two or three consecutive arterial punctures were sometimes necessary before a fairly stable normotensive level was reached. This was especially true in high-spirited dogs. Frequently the pressure was high during the first (up to 280 mm. Hg), but fell abruptly by the time a second puncture was made. In the presence of noise or a strange observer or if the dog had been handled infrequently, the pressure might remain elevated after four consecutive punctures (over a period of 45 minutes).

Because of the marked influence of slight disturbances on these dogs, we studied the effect of measuring the blood pressure in the animal quarters, outside the dog's cage. In this noisy environment the readings were always above the normotensive range (30 to 100 mm. Hg above values obtained in the quiet room). One dog had been denervated by another investigator and observed by him to be hypertensive (220 mm. Hg) 3 months after denervation, when measurements were made in the animal quarters. For one month thereafter we found that in a quiet room, although the initial pressures were 210 to 280 mm. Hg, the final pressures of the first to third arterial punctures were 110 to 155 mm. Hg.

4. The intracisternal injection of cellophane suspensions did not produce a significant hypertension in two dogs, although in one dog

a moderate, temporary elevation of blood pressure occurred following subsequent ligation of the cranial arteries and the occurrence of a cerebral vascular accident.

5. Constriction of the renal arteries according to the technique of Goldblatt was carried out in seven dogs previously injected with kaolin. There was nothing unusual in the behavior of the animals to this procedure which could be attributed to the previous kaolin injection. Four dogs survived successful constriction of both renal arteries. A sustained elevation of arterial pressure resulted in each case (30 to 70 mm. Hg).

V. Evaluation of Indirect Methods of Measuring Blood Pressure in the Dog

The finding of only a slight temporary alteration of mean arterial blood pressure in dogs following intracisternal kaolin injection is in sharp contrast to the marked hypertension reported by others. However, in the dog we have used direct arterial puncture to measure the blood pressure, whereas previous investigators, without exception, used indirect, cuff methods. In order to evaluate the results of these investigators, an extensive study of the characteristics of the indirect blood pressure methods in the dog was made.

Since information was not available in most instances to indicate the particular indirect methods used in published work on kaolin hypertension, four methods which probably had been used were tested in this investigation. Many possible variations of the indirect methods were found to exist. Many of these variations had a considerable influence on the values obtained for the blood pressure. Likewise, numerous technical difficulties and sources of error were encountered in the application of the indirect methods in the dog.

Comparisons of pressure readings taken simultaneously by indirect methods and by direct arterial puncture were made in dogs with sectioned buffer nerves. The hyperlability of the blood pressure in these dogs made it possible to obtain comparisons over a wide range of pressure in a short period of time. It was found that the end point for the maximum reading obtained with indirect methods (used as criterion of hypertension in previous work on kaolin hypertension) was determined by the intravascular systolic pressure. However, the indirect reading was rarely an accurate determination of the latter. In a few instances the indirect readings tended to parallel fairly closely the intravascular systolic pressure at different blood pressure levels. In most instances this was not true. The relationship was different in different dogs and varied with the particular technique and apparatus used.

In fifteen dogs blood pressure was measured for periods of months by both indirect methods and by direct arterial puncture. The indirect methods frequently were found to be unreliable. In several instances it was possible to obtain a considerable elevation of readings with the indirect methods, although little or no change in the direct mean blood pressure level occurred.

DISCUSSION

In the work presented in this thesis an attempt was made to produce experimental neurogenic hypertension by injection of kaolin suspensions into the cisterna magna in the rat, rabbit, and dog. Numerous investigators have reported that this procedure in the dog produces in a rather large percentage of animals a marked elevation of blood pressure which persists from several months to over one year. It has been pointed out previously that the latter investigators used, exclusively, indirect methods of measuring blood pressure. In the experiments described in the present report, wherein direct arterial puncture was used to measure the mean blood pressure, a significant persistent hypertension did not occur in the dog following kaolin injection. The only alteration of blood pressure observed was a rather slight elevation in some dogs which lasted at the most for a few weeks.

While this work was still in progress, it gained strong support from a report of Foa', List, and Peet that they had been unable to produce a significant hypertension by intracisternal kaolin injection in dogs. These investigators also had used direct arterial puncture to measure the blood pressure. Fourteen dogs were injected with kaolin. Only four of the nine dogs that survived showed a slight elevation of mean blood pressure (30-39 mm. Hg) which lasted no longer than 20 days. Later, in a personal communication, Page stated that he, likewise, had been unable to produce kaolin hypertension in dogs, although more than 16 dogs had been injected. He, also, had measured blood pressure by femoral artery puncture.

A review of the procedures used by those who have reported the occurrence of hypertension following kaolin injection does not reveal any significant difference from the techniques used in the present investigation. The type, amount, mode of preparation, and the technique of injection of the kaolin suspensions have been those recommended for the production of hypertension in dogs. Variations of these procedures also were tried. None of these had any different action. In fact the lack of emphasis upon or adherence to any particular aspect of technique in the many publications on "kaolin hypertension" seems to indicate that no particular precautionary measures were encountered. In view of this, one would expect that, in the over fifty dogs injected with kaolin here and by Foa' *et al.*

and Page, a prolonged significant elevation of mean arterial blood pressure would have occurred, if such a possibility existed.

Although the dogs in the present investigation did not develop a significant, persistent elevation of mean arterial pressure, their response in other respects to kaolin injection was like that described in the literature for dogs said to have developed "kaolin hypertension." The signs of irritation of the central nervous system, the increased excitability, the changes in pulse rate, and the disturbances of locomotion described by others were observed in the dogs in this investigation. The occurrence of increased intracranial pressure and the autopsy appearance, including the presence of internal hydrocephalus, likewise have duplicated those described in the literature.

That the dogs used in this investigation were not refractory to the development of arterial hypertension is indicated by the fact that they responded as normal animals to other procedures. Previous injection of kaolin and cavitation of the spinal cord did not prevent the dogs from developing sustained hypertension following constriction of the renal arteries or marked temporary elevations of blood pressure following section of the carotid sinus and aortic nerves.

Thus, aside from the absence of any significant change in the blood pressure, the only apparent difference between our methods and results and those of others was in the method of measuring blood pressure. In the dog we have used direct puncture of the femoral artery, whereas previous investigators have, without exception, used indirect cuff methods.

In an extensive study of the characteristics of the indirect blood pressure methods in the dog these methods were frequently found to be unreliable. In several instances it was possible, using both indirect and direct methods in the same dog, to obtain a considerable elevation of readings with the indirect method, although little or no change in the direct mean blood pressure occurred. These experiments suggest that the actual response of the blood pressure in this investigation and in those of Dixon and Heller and others was more or less identical and that the apparent differences noted are characteristic of the methods used to measure the blood pressure. The following factors may have been involved:

1. The maximal pressure measured by indirect methods is determined by the intravascular systolic pressure. The systolic pressure is subject to wider fluctuations and is elevated more as a result of emotional disturbance than is the mean pressure, which was measured directly in this investigation and by Foa' *et al.* and Page. Indirect diastolic pressure measurements were reported by only two previous investigators. Giordano and Galigani found no change of diastolic pressure in spite of a marked elevation of systolic pressure following kaolin injection. In Vogt's observa-

tions the elevation of diastolic pressure was much less than that of the systolic pressure.

2. The relationship of the indirect readings to the intravascular pressure may be altered under certain conditions. Thus, in the one check of their indirect method reported by Braun and Samet (4), the indirect systolic reading was below the directly measured mean pressure before denervation of the buffer nerves, but was above the mean pressure after the denervation. The elevation of the mean pressure measured directly was slight; the elevation of indirect readings was marked. A similar occurrence was noted in the present investigation.

3. The conditions under which the blood pressure measurements are made affect the readings obtained. Pressure measurements in this investigation were made with careful handling of the dog in a quiet room. Disturbances in the environment or in the handling of the dog result in higher readings being obtained when the dog has been made more excitable or its blood pressure more labile by some experimental procedure. Furthermore, this effect is greater on the systolic than on the mean pressure readings. There is no information about the occurrence of these factors in the reports of previous investigators.

Final proof or disproof of the contention expressed above undoubtedly must await further investigation by those who have reported the successful production of "kaolin hypertension." These investigators, in dogs which they maintain have an arterial hypertension when the blood pressure has been measured indirectly, must determine the response by one of the accepted direct methods, giving consideration not only to the technique, but also to the environment in which measurements are made.

The failure of cardiac hypertrophy and arteriolar changes to occur in the kaolin-injected dogs described in the literature (18, 11, 31) can not be used as a good indication that a significant arterial hypertension did not exist in these dogs. These changes have not been demonstrated conclusively to occur in dogs with benign hypertension resulting from constriction of the renal arteries.

The blood pressure reaction of rats and rabbits to intracisternal kaolin injection was somewhat similar to that in the dog. Very slight transient elevations of pressure were seen in occasional animals, but these can not be considered significant. Especially is this true in the rabbit, which is subject to mild sporadic elevations of blood pressure as a result of spontaneous nephritis. The failure of kaolin hypertension to develop in the rat and rabbit, as in the case of the dog, can not be correlated with the absence of any of the particular pathologic processes reported in kaolin hypertensive animals in the literature. In this respect it should be noted that Lindauer and Griffith failed to obtain kaolin hypertension in

the cat, although increased intracranial pressure and internal hydrocephalus occurred.

Whether the occurrence of temporary hypertension in rats studied by Griffith and the failure of a significant hypertension to develop in the rats in the present study can be explained on the basis of a difference in blood pressure methods can not be stated. Both methods are indirect. However, while the technique developed here for the capillary flow method of Griffith (13) was unsatisfactory, the tail plethysmograph method which was used gave consistent results and was satisfactory in demonstrating renal hypertension in the rat.

Griffith's results have not been confirmed in any published report. However, in a personal communication, Grollman states that he obtained a moderate, temporary elevation of blood pressure in a few rats by kaolin injection. He used the tail plethysmograph method of measuring blood pressure in the unanaesthetized rat. The elevation of pressure in his rats was slight as compared with the marked hypertension reported by Griffith.

SUMMARY

No significant elevation of arterial pressure was observed in rats, rabbits, and dogs following the intracisternal injection of kaolin suspensions. Slight, transient elevations of pressure (less than 30 mm. Hg) occurred in occasional animals. The procedures used and the other signs observed, including changes in pulse rate, increased intracranial pressure, and internal hydrocephalus have duplicated those described in the literature for animals with so-called kaolin hypertension. Evidence is presented which indicates that the production of so-called kaolin hypertension in dogs by others depended on the use of indirect blood pressure methods. Most probably kaolin hypertension as a significant, persistent elevation of arterial blood pressure does not exist or is extremely rare.

Marked softening and cavitation in the cervical region of the spinal cord was observed as a result of adhesive arachnoiditis following intracisternal kaolin injection in rabbits and dogs.

Following section of the buffer nerves in dogs, the blood pressure was markedly unstable, but attained a normotensive level when measured in a quiet room. When measured in the animal quarters it remained at a hypertensive level. On the basis of these observations the difference of opinion which exists in the literature as to whether section of the modulator nerves produces a permanent hypertension in dogs can be explained by a difference in the technique of measuring blood pressure and/or in the conditions under which it is measured.

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VITA

The author was born in Minneapolis, Minnesota, on August 30, 1915. He attended elementary schools in several midwestern towns and high school at the Riverside-Brookfield High School in Riverside, Illinois. His premedical education was obtained at the Morton Junior College in Cicero, Illinois (1932-1934). His medical and graduate education was obtained at the College of Medicine of the University of Illinois (B.S. in 1936, M.S. in Physiology in 1938, M.D. in 1939). Following an internship at the Michael Reese Hospital in Chicago in 1938-1939, he continued his graduate studies in physiology at the University of Illinois. Part of his graduate work was done with the aid of a Research Fellowship in Physiology granted by the University of Illinois (1940-1941). From April, 1941, to December, 1942, he was employed as an instructor in biological sciences and director of health at the Herzl Junior College in Chicago. From December, 1942, to October, 1943, he was employed as a physiologist on O.S.R.D. project OEMcmr-234 at the University of Illinois, College of Medicine. Since October, 1943, he has been employed as a physiologist on O.S.R.D. project OEMcmr-129 in the Acceleration Laboratory of the Mayo Aero Medical Unit, Rochester, Minnesota.

He has been a co-author in the following publications:

Influence of Carbon Dioxide upon the Blood Pressure Reaction to Oxygen Deficiency. With E. Gellhorn. Proc. Soc. Exp. Biol. and Med. 36:169, 1937.

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